REMARKS

Claims 1-7 have been rejected solely under 35 USC § 103 as being unpatentable over Gokarn *et al.*, WO 02/26933 ("Gokarn") in view of Yoshida *et al.*, "*Production of Ubiquinone-10 Using Bacteria*," Journal of General and Applied Microbiology, vol. 44, no. 1, pp. 19-26 (1998) ("Yoshida") and Berry *et al.*, WO 02/099095 ("Berry"). (Paper No. 20070528 at 3).

The rejection respectfully is traversed.

Gokarn discloses "culturing a cell under conditions wherein the cell produces [an] isoprenoid, wherein the cell contains at least one exogenous nucleic acid that encodes at least one polypeptide, wherein the cell produces more of the isoprenoid than a comparable cell lacking the at least one exogenous nucleic acid." (Page 8, lines 12-25). Gokarn further discloses that "[t]he cell can be a *Rhodobacter* or *Sphingomonas* cell," and "[t]he isoprenoid can be CoQ(10)." (*Id.*). "The at least one polypeptide can have DDS, DXS, ODS, SDS, DXR, 4-diphosphocytidyl-2C-methy-l-D-erythritol synthase, 4-diphosphocytidyl-2C-methyl-D-erythritol kinase, or chorismate lyase activity. The at least one polypeptide can be a UbiC polypeptide or a LytB polypeptide." (*Id.*).

Yoshida discloses "three strains, *Agrobacterium tumefaciens* KY-3085 (ATCC4452), *Paracoccus denitrificans* KY-3940 (ATCC19367) and *Rhodobacter sphaeroides* KY-4113 (FERM-P4675)" as "excellent producers" of CoQ10. (Abstract and page 19). ***Such strains were obtained by random mutagenesis and selection.*** (Pages 20-24).

Berry discloses "[i]solated polynucleotides encoding polypeptides having the activity of enzymes in the mevalonate pathway, *e.g.* hydroxymethylglutaryl-CoA reductase, isopetenyl diphosphate isomerase, hydroxymethylglutaryl-CoA synthase, mevolante kinase, phosphomevalonate kinase, or diphosphomevalonate decarboxylase." (Abstract). Berry further discloses that these enzymes are "useful for recombinantly producing . . . carotenoids like phytoene, lycopene, β-carotene, zeaxanthin, canthaxanthin astaxanthin, adonixanthin, cryptoxanthin echinenone and adonirubin." (*Id.*).

In making the rejection, the Examiner asserted that Gokarn discloses "the identification of polynucleotide sequences involved in isoprenoid production and also use of the *Rhodobacter sp.,* microorganism for the production of CoQ10 by introducing heterologous genes involved in the isoprenoid production (CoQ10), including transformation procedures in said microorganism (lines 13-29, page 8; lines 10-34, page 9; pages 45-51; Examples 5, 8 and 14; Fig. 1)." (Paper No. 20070528 at 3).

The Examiner acknowledged, however, that Gokarn "is silent regarding production of CoQ10 in *Rhodobacter sp.,* by transforming said microorganism with a plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens*." (*Id.*).

To fill the acknowledged gap, the Examiner relied on Yoshida for "disclos[ing] [ ] *Rhodobacter sphaeroides* as an excellent producer and host for the production of ubiquinone-10 (CoQ10), an isoprenoid compound (Abstract and Introduction section, page 19)." (*Id.*). The Examiner further relied on Berry for "disclos[ing] the sequence of plasmid pBR-K-mev-op-R114, comprising a mevalonate

operon of *Paracoccus zeaxanthinifaciens* strain ATCC 21588, wherein said mevalonate operon comprises polynucleotides that encode MvaA (hydroxymethyglutaryl-CoA reductase), Idi (isoprenyl diphosphate isomerase), Hcs (hydroxymethyglutaryl-CoA synthase) Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase) and Mvd (diphosphomevalonate decarboxylase) ...." (*Id.* at 3-4).

The Examiner then contended that "it would have been obvious to a person of ordinary skill in the art to combine the teachings of Gokarn et al., Yoshida et al., and Berry et al., to generate a recombinant *Rhodobacter sphaeroides* comprising a mevalonate operon of *Paracoccus zeaxanthinifaciens* as such a recombinant would produce enhanced levels of CoQ10." (*Id.* at 4). The Examiner also contended that "[t]he above-mentioned references teach all the elements of the instant application, including motivation and expectation of success. Gokarn et al., and Yoshida et al., provide the motivation to use *Rhodobacter* for the reasons cited above and Berry et al., teach the isolation of pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* comprising the structural elements of the instant invention for the production of CoQ10." (*Id.* at 5).

Initially, we note that the Examiner has withdrawn the previous §103 rejection over Berry in view of Hahn, Gokarn, and Yoshida. (Paper No. 20061031 at 9). The Examiner has now recast the rejection as Gokarn in view of Yoshida and Berry. (Paper No. 20070528 at 3). However, if the claims were not obvious over the ***four*** previously cited references (Berry in view of Hahn, Gokarn, and Yoshida) then certainly they are not obvious over ***three*** out of the ***four*** previously cited references (Gokarn in view of Yoshida and Berry).

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added).

Here, the rejection is devoid of *any* evidence - or even argument - in support of the proposed combination. All that is there are conclusory remarks and a conclusory statement that "[t]he above mentioned references teach all the elements of the instant application including motivation and expectation of success." (Paper No. 20070528 at 4-5). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Gokarn using

Yoshida and Berry to arrive at the claimed invention. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

Assuming *arguendo* that Gokarn is properly combinable with Yoshida and Berry, which it is not, such a combination does not produce the process of the

previously amended claims. The Examiner has already acknowledged that Gokarn "is silent regarding production of CoQ10 in *Rhodobacter sp.*, by transforming said microorganism with a plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens*." (Paper No. 20070528 at 3). Gokarn also fails to disclose or suggest the claimed mevalonate operon. As discussed in our previous response, independent claims 1, 4, and 5 were amended to recite a process "wherein the mevalonate operon comprises polynucleotides that encode ***MvaA (hydroxymethylglutaryl-CoA reductase), Idi (isopentenyl diphosphate isomerase), Hcs (hydroxymethylglutaryl-CoA synthase), Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase), and Mvd (diphosphomevalonate decarboxylase)***."

Moreover, the Examiner's reliance on Berry for "disclos[ing] the structural element of the instant invention sequence of plasmid pBR-K-mev-op-R114" to the exclusion of all of Berry's other disclosure is ***against*** well established precedent. "A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 (8th ed. Rev. 5, August 2006, p. 2100-124). Simply put, the Examiner has failed to consider Berry in its entirety. Berry discloses over expression of ***endogenous*** mevalonate pathway genes whereas the presently claimed process relates to the ***heterologous*** expression of the mevalonate pathway genes from the genus *Paracoccus* in the genus *Rhodobacter*. Here, the claimed process has nothing to do with the ***endogenous*** mevalonate pathway that is disclosed in Berry. Furthermore, Berry is concerned with the enhanced production of carotenoid compounds. Berry discloses that over expression of the ***endogenous*** mevalonate operon results in enhanced production of carotenoids and their precursors. But the rejection fails to identify where Berry

discloses the overproduction of coenzyme Q10 as claimed. Thus, the rejection does not - and cannot - identify where in Berry there is disclosed ***the use of heterologous sequences in a host microorganism as claimed***.

The Examiner has yet to come to grips with these glaring factual differences. It is respectfully submitted that Berry and Gokarn do not disclose or suggest claims 1-7. Unfortunately for the Examiner, Yoshida does not fill the factual gaps left by Gokarn and Berry. Yoshida discloses the production of coenzyme Q10 by three specific bacterial strains (*Agrobacterium tumefaciens KY-3085* (ATCC4452), *Paracoccus denitrificans* KY-3940 (ATCC19367) and *Rhodobacter sphaeroides* KY-4113 (FERM-P4675)). These three strains are part of a strain collection from Kyowa Hakko Kogyo Co, Ltd. As one skilled in this art would recognize, all three strains were obtained by ***random mutagenesis and selection*** for higher coenzyme Q10 production using a treatment with N-methyl-N'-nitro-N-nitrosoguanidine. Yoshida discloses that that these selected strains were largely improved in their capacity to produce coenzyme Q10 compared to the wild type strains. Therefore, at best, Yoshida teaches that *A. tumefaciens, P. denitrificans* and *R. sphaeroides* could be "excellent producers of coenzyme Q-10" if one could improve their production by ***random mutagenesis and selection***.

At bottom, one would not look to Yoshida for ideas/methods to use in engineering a bacterial strain as is presently claimed. Therefore, Yoshida is at best non-analogous art and can not be cited (*see* MPEP § 2141.01(a) (8th ed. Rev. 5, August 2006, p. 2100-119)) and at worst is irrelevant to the present claims.

Thus, none of the Examiner's secondary references fill the gaps left by Gokarn. Hence, the proposed combination of Gokarn, Yoshida, and Berry falls short of disclosing or suggesting the currently claimed invention. In view of the foregoing, it is

respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Accordingly, for the reasons set forth above, reconsideration, withdrawal of the rejection, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on October 3, 2007.

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